HAUTE AUTORITÉ DE SANTÉ

ONCOLOGY
New indication
March 2017

BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION

GAZYVARO (obinutuzumab), monoclonal antibody

No clinical benefit demonstrated in combination with bendamustine followed by Gazyvaro maintenance for the treatment of patients with follicular lymphoma who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen

Main points

- GAZYVARO now has Marketing Authorisation as part of a therapeutic strategy in patients with follicular lymphoma (FL) who did not respond or who progressed during or up to 6 months after treatment with rituximab or a rituximab-containing regimen.
- The therapeutic strategy of GAZYVARO + bendamustine (induction) followed by maintenance treatment with GAZYVARO improved progression-free survival compare to treatment with bendamustine alone in patients with indolent non-Hodgkin lymphoma in early relapse and in patients with follicular lymphoma.
- No improvement in overall survival has been demonstrated.
- Many issues have been raised regarding the study design which could favor the GAZYVARO arm relative to the bendamustine arm.

Pre-existing indication*

GAZYVARO already has Marketing Authorisation in the treatment of chronic lymphocytic leukaemia.

Therapeutic use

Treatment for FL relapse depends notably on the treatment line(s) previously received, the type and duration of the remission and the spread of the disease. According to European recommendations, the therapeutic options are chemotherapy, immunochemotherapy, radioimmunotherapy and allogeneic stem cell transplant in eligible subjects. Rituximab should only be added if the prior treatment based on rituximab led to achieving patient remission greater than 6 months and obinutuzumab could be used.
American guidelines recommend, in order of preference, immunochemotherapy, rituximab± lenalidomide, radioimmunotherapy and idelalisib. Rituximab, stem-cell transplant and obinutuzumab can also be used in maintenance treatment.
According to French expert opinion, resumption of rituximab in combination with chemotherapy, regardless of the duration of remission from the preceding line, may be proposed, although there is no consensus on retreatment with rituximab in case of failure.

- **Role of the proprietary medicinal product in the therapeutic strategy**
  GAZYVARO in combination with bendamustine in induction, followed by a GAZYAVRO maintenance treatment, is a supplemental second-line or later therapeutic strategy in patients with FL who did not respond or who progressed during or up to 6 months after treatment including rituximab.

Clinical data

- An open-label, randomised study compared induction treatment either with bendamustine alone (arm B, n=202) or by the combination of obinutuzumab + bendamustine (arm GB-G; n=194) for 6 cycles of 28 days. At the end

* This summary does not cover this indication.

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of the induction period, arm GB-G patients who had a complete or partial response or stable disease continued to receive obinutuzumab in monotherapy every two months for two years, or until progression, as a maintenance treatment. Patients of arm B did not receive maintenance treatment. Bendamustine was administered at a dose of 90 mg/m^2/day in arm GB-G and 120 mg/m^2/day in arm B.

A total of 396 patients with indolent non-Hodgkin lymphoma who did not respond or who progressed during or up to 6 months after treatment with a rituximab-containing regimen were included. A total of 81% of patients included presented LF. Marketing Authorisation has only been granted in this subgroup.

- After a median follow up of 21 months, the median progression-free survival (primary endpoint) was 14.9 months in the induction by bendamustine alone arm, and not reached in the induction with bendamustine + obinutuzumab followed by maintenance treatment with obinutuzumab arm (HR=055; 95% CI [0.40; 0.74]; p=0.0001). The results in the subgroup of patients with FL were comparable (HR=0.48; 95% CI [0.34; 0.68]; p<0.0001).
- No statistically significant difference was observed in the amount of patients who presented a complete or partial response as best response observed (76.6% in arm B versus 78.6% in arm GB-G, NS). Because the endpoints were hierarchized beforehand in the protocol, it is not possible to conclude on the other endpoints, especially overall survival.
- The study design can be criticised because it only permits comparing two therapeutic strategies (GB-G versus B) and not determining the supplemental effect of adding GAZYVARO compared to bendamustine alone in induction. We also cannot know if the effect observed on the reduction in the risk of progression, relapse or death of 45% in the GB-G arm is provided by induction, maintenance or both. It would have been desirable to be able to assess the specific effect of the addition of GAZYVARO in induction relative to bendamustine alone, and then, in a second stage, to assess the specific effect of maintenance with GAZYVARO versus a comparator left to the discretion of the investigator.
- Although the safety follow-up data are limited in FL, the nature, frequency and severity of adverse reactions conformed to the safety profile observed in patients with CLL.

Special prescribing conditions

- Medicine for hospital prescription and restricted to haematologists or doctors trained in blood diseases.
- Medicine requiring special monitoring during treatment

Benefit of the medicinal product

- The actual clinical benefit* of GAZYVARO combined with bendamustine in induction, followed by GAZYVARO maintenance treatment is substantial.
- GAZYVARO, combined with bendamustine in induction, followed by GAZYVARO maintenance treatment does not provide clinical added value** (CAV V) in the treatment strategy.
- Recommends inclusion on the list of reimbursable products for hospital use.

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This document was created on the basis of the Transparency Committee Opinion of 08 March 2017 (CT-15477) and is available at **www.has-sante.fr**

* The actual clinical benefit (ACB) of a medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the ACB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means “no clinical added value”.

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